REMARKS

Status of Claims

Claims 92 and 129-131 are currently pending. Claim 92 has been amended. Claims 129-131 have been added. Support for the amended and added claims is found throughout the specification as originally filed, *inter alia*, in the following: Examples 8-15; claims as originally filed; page 22, and Figure 5. Accordingly, Applicants submit that no new matter is introduced into the specification by way of the present amendments pursuant to 35 U.S.C. § 132. Applicants respectfully request entry of the amendments, reconsideration of the rejections, and allowance of the pending claims.

Claims 1-91 and 93-128 have been canceled without prejudice or disclaimer as to the claimed subject matter pursuant to the restriction requirement or otherwise solely to expedite prosecution of the present application. Applicants reserve the right to pursue canceled subject matter in one or more continuation or divisional applications, as appropriate.

Claim Objections

Claims 92-94, 98-106, and 128 are objected. Applicants respectfully submit that the present claim amendments obviate these claim objections. Reconsideration of the claim objections is requested in view of the present claim amendments.

35 U.S.C. § 101

Claim 105 is rejected under 35 U.S.C. § 101. Applicants disagree with this rejection. The present claim amendments, however, cancel claim 105, thereby rending this rejection moot. Withdrawal of this rejection is respectfully requested.

35 U.S.C. § 112, first paragraph - written description

Claims 92-94, 98-106, and 128 are rejected for allegedly failing to meet the written description requirement under 35 U.S.C. § 112, first paragraph. Applicants disagree with this rejection. The present claim amendments, however, obviate this rejection. Claims 93-94, 98-106, and 128 have been canceled, thereby rending this rejection moot with regard to these claims. Claim 92 has been amended to recite a polypeptide comprising an amino acid sequence having at least 95 % identity to the amino acid sequence of SEQ ID NO: 4.

Example 10 of the Written Description Guidelines Revision 1[1/] provides useful guidance in determining what scope of claims would be allowable with respect to the written description requirement. Example 10 considers the following hypothetical claim:

> Claim 2. An isolated variant of a protein comprising the amino acid sequence shown in SEQ ID NO: 3, wherein the variant comprises an amino acid sequence that is at least 95% identical to SEQ ID NO: 3.

The example explains that because the specification adequately describes proteins comprising the amino acid sequence of SEQ ID NO: 3, the specification also adequately describes proteins that are at least 95% identical to SEQ ID NO: 3. That is because all of the species within the genus share a significant degree of partial structure (*i.e.*, at least 95% of SEQ ID NO: 3). The example also explains that the claimed variants can have amino acid substitutions, deletions, insertions, or additions, as compared to SEQ ID NO: 3. This is because those skilled in the art would expect members of the genus to have properties similar to those of SEQ ID NO: 3, because of the high degree of structural similarity. Specifically, the PTO concludes that the hypothetical claim provides adequate written description for the following reasons:

> The specification adequately describes proteins comprising the amino acid sequence of SEQ ID NO: 3 (see the analysis of claim 1). All of the proteins within the scope of claim 2 share at least 95% of the amino acid sequence of SEQ ID NO: 3; therefore, the specification describes 95% of the structure that defines the proteins within the claimed genus. All of the species within the genus share a significant degree of partial structure (i.e., at least 95% of SEQ ID NO: 3).
>
> The claimed variants can have amino acid substitutions, deletions, insertions, or additions, as compared to SEQ ID NO: 3. The specification does not provide an actual reduction to practice of any variants of the protein of SEQ ID NO: 3. The specification does not describe the complete structure or physical or chemical properties of any variants of SEQ ID NO: 3, although those skilled in the art would expect members of the genus to have properties similar to those of SEQ ID NO: 3, because of the high degree of structural similarity.
>
> In view of the disclosure of SEQ ID NO: 3, those skilled in the art could readily envision all of the amino acid sequences that are 95% identical to SEQ ID NO: 3. Those skilled in the art could recognize amino acid sequences that are 95% identical to SEQ ID NO: 3 by comparing a given sequence to SEQ ID NO: 3. The presence of an amino acid sequence that is at least 95% identical to SEQ ID NO: 3 is a structural feature of each of the proteins within the claimed genus.

[1/] Revision of March 25, 2008 available at http://www.uspto.gov/web/menu/written.pdf.

> The level of skill and knowledge in the art is such that one of ordinary skill would be able to make and identify variants having 95% identity to SEQ ID NO: 3 routinely.
>
> Thus, those skilled in the art would have recognized the disclosure as showing that the applicant was in possession of the claimed genus of protein variants at the time of filing.

Thus, Example 10 of the Guidelines teaches that the requirement for written description is satisfied where all variants are structurally similar to a particular sequence, *i.e.*, at least 95% identical. Applicants respectfully submit that the scope of the claims include NsG33 polypeptides that are structurally similar— that is, the claims recite NsG33 polypeptides that are at least 95% identical to SEQ ID NO: 4 and having the conserved cysteine residues at positions 7, 28, 59, 95, 148, 151, 161, 219, 243, and 265 relative to the amino acid sequence of SEQ ID NO: 4.

Finally, the assertion on page 4 of the Office Action that a person of ordinary skill in the art "cannot visualize or predict what critical amino acid residues would structurally characterize the genus of [claimed] polypeptides" is not factually supported. For example, Figures 3 and 5 show multiple sequence alignments of human, mouse and rat proteins having strongly conserved cysteine residues at positions 7, 28, 59, 95, 148, 151, 161, 219, 243, and 265 relative to the amino acid sequence of SEQ ID NO: 4.

In view of the above, Applicants respectfully request withdrawal of this rejection.

35 U.S.C. § 112, first paragraph- enablement

Claims 92-94, 98-106, and 128 are rejected for allegedly failing to meet the enablement requirement under 35 U.S.C. § 112, first paragraph. Claims 93-94, 98-106, and 128 have been canceled, thereby rending this rejection moot with regard to these claims. Claim 92 has been amended to recite a method of treating Huntington's disease and neuropathic pain. The present claim amendments obviate this rejection.

The specification provides experimental data that supports the enablement of the present claims. NsG33 is expressed at high levels in the central midbrain in the putamen (see Example 5), and the degeneration of these neuronal populations are associated with Huntington's disease. The expression data is combined with the results of the bioinformatics

analyses and the neuroprotective/neurogenesis activity of NsG33, in particular Example 15. Example 15 describes an *in vitro* model were striatal cultures were contacted with human NsG33. As taught by the Specification (see *e.g.,* Abstract), NsG33 is a secreted polypeptide. Thus, the cells are exposed to NsG33 conditioned media (administered via secretion from the transfected cells), which showed the increased survival of rat striatal cultures (Figure 12). Huntington's disease is a genetic neurodegenerative disorder characterized clinically by degeneration of striatal neurons, and the use of striatal cultures as an *in vitro* model for Huntington's disease is well established in the art.[2/] The experimental data provided of Figure 12 and Example 15 shows the increased survival of striatal cultures in the presence of NsG33. According, the data provided in the specification (*e.g.*, in Examples 5 and 15 and Figure 12) support enablement of the use of NsG33 for use in a method to treat Huntington's disease.

Jørgensen[3/] confirms the neuroprotective and regenerative activity of NsG33 in striatal neurons. Jørgensen teaches the *in vivo* delivery of NsG33 (METRN) into the striatum via direct injection or via a lentiviral vector. See *e.g.,* Figure 6 and discussion related thereto. These studies showed that NsG33 is a highly diffusible molecule in the brain and cellular uptake was demonstrated in the striatum. According, the data provided in Jørgensen supports enablement of the use of NsG33 for use in a method to treat Huntington's disease. A copy of Jørgensen is attached hereto and Exhibit A.

With regard to neuropathic pain, NsG33 is expressed at high levels in the dorsal root ganglion (DRG) (see Example 5), and the degeneration of these peripheral neuronal populations are associated with neuropathic pain. Specifically, neuropathic pain is associated with sympathetic postganglionic nerve fiber sprouting in the dorsal root ganglion.[4/] The expression data of Example 5 of the specification is combined with the results of the

---

[2/] See *e.g.*, Oliveira *et al.*, "Mitochondrial-dependent Ca2+ handling in Huntington's disease striatal cells: effect of histone deacetylase inhibitors;" *J Neurosci.* 2006 Oct 25;26(43):11174-86. PubMed PMID: 17065457.

[3/] *J. Mol. Neurosci.* 39(1-2):104-16 (2009).

[4/] See *e.g.*, Todoroki *et al.*, "Ropivacaine inhibits neurite outgrowth in PC-12 cells;" *Anesth Analg.* 2004 Sep;99(3):828-32. PubMed PMID: 15333418.

bioinformatics analyses and with the neuroprotective/neurogenesis activity and antiapoptotic effect of NsG33 (Examples 6, 14 and 15). In particular, Figure 9, Example 6, and the section encompassed on page 15, line 18 to page 16, line 24 demonstrate biological activity of NsG33 in a PC12 assay using serum-free medium. This assay can be considered as a general assay for testing of protection against excitotoxic damage. The data presented in the specification thus shows the neuroprotective effect of NsG33 on PC12 cells.

Sympathetic axonal sprouting in dorsal root ganglia has been shown to be a major phenomenon implicated in neuropathic pain. Importantly, the use of PC12 cells as an *in vitro* model for neuropathic pain and cellular model of sympathetic sprouting is well established in the art. For example, Todoroki teaches that PC12 cells has "achieved preeminence as a cellular model of sympathetic sprouting" and therefore is used as a model for neuropathic pain.[5/] A copy of Todoroki is attached as Exhibit B. According, the data provided in the specification (*e.g.*, in Example 5 and 6) support enablement of the use of NsG33 for use in a method to treat neuropathic pain.

The Specification discloses that the assay of Example 9 may be used to verify neuroprotective/neurogenesis activity of NsG33 and use in the treatment of peripheral neuropathies.[6/] The data presented in Figure 5D of Jørgensen demonstrates axonal sprouting in dorsal root ganglion explants and is confirmation of the assay described in Example 9 of the Specification. Jørgensen confirms that NsG33 induces axonal sprouting in dorsal root ganglion with potency comparable to that of NGF, which is a candidate for treatment of neuropathic pain. Figure 3 of Nishino[7/] further supports enablement of the present claims and shows that NG33 promotes axonal extension in the dorsal root ganglion. A copy of Nishino is attached as Exhibit C.

[5/] See *e.g.*, Todoroki *et al.*, "Ropivacaine inhibits neurite outgrowth in PC-12 cells;" *Anesth Analg.* 2004 Sep;99(3):828-32. PubMed PMID: 15333418.

[6/] See Specification at page 41, lines 33-37 to page 42, lines 1-9.

[7/] Nishino *et al.*; "Meteorin: a secreted protein that regulates glial cell differentiation and promotes axonal extension. EMBO J. 2004 May 5;23(9):1998-2008. Epub 2004 Apr 15.

In summary, the present inventors have demonstrated the neuroprotective effect of NsG33 in cellular models for Huntington's disease and neuropathic pain. The data presented herein thus provides specific evidence that refutes the general arguments presented in the Office Action. Accordingly, applicants respectfully submit that the rejection is not supported by acceptable evidence that the claimed invention is inconsistent with enablement. At best, the Office Action sets forth broad allegations that the disclosure is speculative and recites various difficulties that might be encountered in practice of the invention. This is not a sufficient evidentiary basis for requiring proof of enablement and a shifting of the burden of proof to applicant. Withdrawal of this rejection is respectfully requested.

35 U.S.C. § 102(b) - WO 01/39786

Claims 92-94, 98-106 and 128 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 01/39786. Applicants disagree with this rejection. WO 01/39786 is relied on for its disclosure of treatment of autoimmune diseases, including multiple sclerosis, with the disclosed polypeptide of SEQ ID NO: 4 (SMAF-2), which is allegedly 100% identical to the recited SEQ ID NO: 3. WO 01/39786, however, does not identify SMAF-2 as a neuroprotective agent and does not expressly teach the use of SMAF-2 in a method of treating Huntington's Disease or neuropathic pain. Accordingly, WO 01/39786 cannot anticipate the present claims. Withdrawal of this rejection is requested.

35 U.S.C. § 102(b) - WO 01/57190

Claims 92-94, 98-106 and 128 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 01/57190. Applicants disagree with this rejection.

WO 01/57190 is relied upon for its disclosure of the polypeptide disclosed as SEQ ID NO: 1401, which is allegedly 100% identical to SEQ ID NO: 3. WO 01/57190 does not expressly teach all the active steps of the present claims. At least, WO 01/57190 does not identify the polypeptide disclosed as SEQ ID NO: 1401 as a neuroprotective agent and does not expressly disclose the use of SEQ ID NO: 1401 in a method of treating Huntington's Disease or neuropathic pain. Rather, WO 01/57190 provides very long and unrelated lists of nucleotide sequences or accession numbers to nucleotide sequences, discloses long lists of

unrelated disorders, and does not provide any guidance as how to elect a specific sequence from the extremely long list of sequences, and how to prepare and apply the elected sequence in order to treat a specific disorder or for a specific use.

Furthermore, WO 01/57190 does not provide any functional data and does not enable any use of the polypeptide disclosed as SEQ ID NO: 1401. M.P.E.P § 2121.01 is instructive on this point and provides as follows:

> The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003) (At issue was whether a prior art reference enabled one of ordinary skill in the art to produce Elan's claimed transgenic mouse without undue experimentation. Without a disclosure enabling one skilled in the art to produce a transgenic mouse without undue experimentation, the reference would not be applicable as prior art.).

Accordingly, withdrawal of this rejection is respectfully requested.

CONCLUSION

An indication of allowance of all claims is respectfully solicited. Early notification of a favorable consideration is respectfully requested. In the event any issues remain, Applicant would appreciate the courtesy of a telephone call to their counsel to resolve such issues and place all claims in condition for allowance.

Respectfully submitted,

Dated: December 23, 2009

By: /Sheridan Snedden/

Ivor R. Elrifi, Reg. No. 39,529
Sheridan K. Snedden, Reg. No. 55,998
Attorneys for Applicants
c/o MINTZ, LEVIN
Tel: (617) 542-6000
Fax: (617) 542-2241
Customer No. 30623